Claim 32: page 5, first full paragraph

II. Objections

Claim 45 is objected to for failure to provide the full name for vWF propeptide. It is submitted that amendment of this claim is not required since it has been withdrawn from consideration as drawn to a non-elected invention.

III. Claim Rejections under 35 U.S.C. 112, Second Paragraph

Claim 32 is rejected for use of the phrase "essentially comprised of," which is said to render the claim indefinite. This claim has been amended so the phrase "essentially comprised of" is replaced with "consisting essentially of." The term has its generally accepted meaning such as indicated at page 5, first full paragraph.

IV. Claim Rejections under 35 U.S.C. 102

A. Currently Claimed Invention

Independent claims 31 and 67 refer to pharmaceutical preparations that comprise vWF propeptide or pro-vWF, respectively (see prior Office Action response for a review of these terms). The preparations have treated for virus removal or inactivation so they are suitable for therapeutic administration; certain preparations are formulated for parenteral administration. Certain preparations include one or more additional components such as a hemostasis protein, a platelet component, or a phospholipid.

B. Burnouf Distinguished

Claims 31-32, 35-37, 39-40, 43-44 and 64-71 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Burnouf-Radosevich et al. (*"Burnouf"*). Articles by Turecek et al. (Blood 94:1637-1647, 1999) (*"Turecek"*), Ruggeri et al. (Thrombosis and Haemostasis 67:594-599, 1992) (*"Ruggeri"*), and Wise et al. (Cell 52:229-236, 1988, at page 229, col. 2, lines 6-8) (*"Wise"*) are cited as evidence of inherent properties of the preparation discussed by

Burnouf. For the reasons that follow, Applicants respectfully disagree that Burnouf anticipates the present claims.

While acknowledging that Burnouf is directed to methods of preparing vWF from a cryoprecipitate, the Examiner continues to assert that a partially-purified preparation obtained during the process of purifying vWF nonetheless contains vWF propolypeptide (i.e., vWF propeptide) and/or pro-vWF and thereby anticipates the foregoing claims. To reach this conclusion the Examiner notes that vWF is initially synthesized as a pre-pro-peptide. Upon cleavage of the signal peptide, pro-vWF (containing the propeptide and mature peptide segments) is said to dimerize and assemble into multimers, with the propolypeptide (vWF propeptide) subsequently removed by proteolytic cleavage. The Examiner notes, however, that the proteolytic cleavage of pro-vWF to form vWF-propeptide and mature vWF is not always complete. And while cleavage of pro-vWF mainly occurs intracellularly, the Examiner points to statements in Turecek and Ruggeri to contend that some incompletely processed pro-vWF is secreted into the circulation where it is cleaved into vWF propeptide and mature vWF (Office Action, page 6). Statements in Wise are also referred to as stating that vWF propeptide itself can be secreted as a distinct protein (Office Action, page 6). It is thus concluded that the Burnouf composition obtained from a plasma cryoprecipitate necessarily contains pro-vWF and vWF propeptide (Office Action, paragraph bridging pages 6 and 7).

As the foregoing analysis is based on properties that are said to be *inherent* to the Burnouf preparation (Office Action page 5, lines 1-2), Applicants reemphasize the point made in the preceding response that the Patent Office must overcome a substantial burden when its arguments hinge on inherent properties. Specifically, the Federal Circuit has said:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not

sufficient.' (MPEP 2112; citing In re Robinson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999) (emphasis added).

Applicants first address the contention that the Burnouf plasma would *necessarily* contain pro-vWF. While the Office Action correctly notes that Turecek and Ruggeri teach that some pro-vWF is secreted into the circulation, it fails to recognize the additional teachings concerning the fate of secreted pro-vWF. Turecek goes on to say that while pro-vWF is secreted into the circulation that it "is detectable in normal human plasma only on rare occasions, and even then only trace amounts are observed" (Turecek at page 1637, col. 2, lines 6-8). This is attributed to the fact that pro-vWF is quickly metabolized in the circulation (Id. at page 1644, 9th sentence from the end of the first column). These two points are reemphasized by recent scientific articles on the processing of pro-vWF, copies of which are enclosed and listed as part of the accompanying supplemental information disclosure statement. (See, Varadi, et al. (2001) Thromb. Haemost. 86:1449-1458, at page 1449, col. 2, 4th sentence of second complete paragraph [*"Varadi"*]; and Turecek et al. (2002) Histochem. Cell Biol., 117:123-129, at page 124, second col., last three sentences [*"Turecek II"*]).

The available evidence then is clear that pro-vWF released into the circulation is rapidly degraded to concentration levels that are rarely detectable. As such, the Burnouf preparation would not *necessarily* contain pro-vWF as posited in the Office Action. This is particularly true given that at least 20 hours is required to obtain the preparation (12 hour thawing process followed by 8 hour solvent-detergent treatment, see Burnouf, col. 5, lines 37 and 61). Any pro-vWF that may have been present at the time of collection would certainly be degraded 20 hours thereafter. To suggest otherwise is contrary to the complete teachings of the foregoing references and at best is only a remote possibility that is not sufficient to satisfy the inherency criterion.

A complete review of the references also makes clear that the Burnouf composition would unlikely contain vWF-propeptide. The Office Action is correct in recognizing that vWF-propeptide can be secreted, but fails to recognize the additional teachings

regarding its fate once secreted. Borchiellini (Blood (1996) 88:2951-2968; cited in the enclosed supplemental information disclosure statement), for example, found that the concentration of vWF-propeptide in collected samples initially is only one-tenth that of mature vWF. Only under inducement of *pathophysiological* conditions was the level of vWF-propeptide increased. But even then the concentration was only about half that of mature vWF (see abstract of Borchiellini; see also Turecek at page 1637, col. 1, last line to col. 2, line 4). Furthermore, vWF-propeptide has a half-life that is substantially less than that for mature vWF (2-3 hours versus 12 hours, respectively) (Turecek at page 1637, col. 1 last line to col. 2, line 4).; see also, Varadi, page 1449, col. 2, first full paragraph). The evidence as a whole then clearly shows that there is no reason to conclude that the Burnouf composition *necessarily* contains pro-vWF, particularly since it takes at least 20 hours, which is equivalent to approximately *7 to 10 vWF half lives*, to obtain the composition.

While these arguments are deemed sufficient on their own to justify a withdrawal of the rejection based on Burnouf, Applicants also address the remaining issues that are discussed in the Office Action. For example, in the prior response Applicants argued that there was no evidence in Burnouf to suggest that pro-vWF or vWF propeptide would remain in solution following the centrifugation and aluminum hydroxide purification steps that are part of the Burnouf purification. The Office discounts this argument since Wise is said to teach that vWF-propeptide and mature vWF are associated with one another. Because of this interaction, it is concluded that the Burnouf preparation must contain vWF-propeptide (Office Action, page 7).

This analysis, however, misses a subtle aspect of the association between vWF-propeptide and mature vWF discussed in Wise. While it is correct that Wise indicates that vWF-propeptide and mature vWF interact with each other *intracellularly* (Wise, page 233, col. 2, lines 3-12), this is *not* the case once the peptides are secreted into the circulation. Wise specifically notes that "[a]lthough both molecules (vWF-KRX and vWF-ΔPro) [i.e., vWF-propeptide and mature vWF obtained following cleavage of the signal sequence] were present in culture medium [i.e., after the peptides were secreted], they were *no longer coprecipitated* by anti-vWF antibodies" (Id. at lines 12-15; emphasis added).

Several sections from the enclosed scientific article by Wagner, et al. (Proc. Natl. Acad. Sci. (1987) 84:1955-1959) ("*Wagner*") explicitly support this conclusion. For example, Wagner makes the following statements:

"In contrast to their common *intracellular* path, vWf and its propolypeptide [i.e., vWF-propeptide] separated after secretion from endothelial cells." (Id. at page 1958, col. 1, first sentence of second paragraph; emphasis added).

"Because of the separate fate of vWf and its propolypeptide *after secretion*, if a role in hemostasis for the propolypeptide were to be found, it is likely to be independent of vWF." (Id. at page 1958, col. 2, last sentence; emphasis added).

The literature teachings then explicitly refute the hypothesis set forth in the Office Action that vWF-propeptide and mature vWF would be associated in the Burnouf preparation. To the contrary, these articles provide evidence that these two peptide would *not* be associated, even in the initial cryoprecipitate. And there is certainly no evidence to suggest that they would be associated following subsequent purification.

Turning now to specific statements regarding pro-vWF, the Office Action (paragraph bridging pages 7 and 8) again refers to sections from Wise to support the proposition that the Burnouf preparation would contain pro-vWF, even following the centrifugation and aluminum hydroxide purification steps. As explained at length in the preceding section, however, any pro-vWF initially present would rapidly be degraded.

Finally, Applicants address the assertion that the Burnouf composition anticipates claim 69 (Office Action, page 6). Apparently referring to conclusions in Wise and perhaps Leyte et al. (Biochem. J. (1991) 274:257-261) (*"Leyete"*), it is argued that vWF-propeptide is required for Factor VIII binding. Because Burnouf states that the composition can contain Factor VIII and the composition maintains Factor VIII binding, it is concluded that pro-vWF inherently must be present in the Burnouf composition.

This argument, however, reflects a misreading of Wise and Leyete. Wise primarily emphasizes that vWF-propeptide is important in forming multimers of pro-vWF or mature vWF. Leyete discusses the possibility that vWF-propeptide is important in directing the folding of the N-terminus of *mature vWF*, which is the binding site for Factor VIII. However, despite these roles, the literature is clear that Factor VIII cannot bind vWF until *after* the vWF-propeptide is cleaved away (see, e.g., Turecek, at page 1637, col. 1, 9th sentence from the end; and Turecek II, at page 124, col. 2, second complete paragraph). In fact pro-vWF is thought to block access of factor VIII to vWF (see, e.g., Turecek, at page 1645, first complete paragraph). So contrary to the conclusion in the Office Action, Factor VIII binding is consistent with the presence of *mature vWF*, not vWF-propeptide, in the Burnouf composition. This of course makes sense as Burnouf focuses on methods for purifying vWF.

C. Takagi Distinguished

Claims 31-32, 39-40, 43-44 and 64-66 are alleged to be anticipated by Takagi et al. (J. Biol. Chem. (1989) 264:6017-6020) (*"Takagi"*). The Office Action specifically contends that Takagi discloses a composition including vWF-propeptide that is isolated from human platelets. With respect to the requirement in the claim that the preparation be treated for at least one of viral inactivation and virus removal, the Office interprets this to mean only that *some* viruses have been removed, as the specification is alleged not to indicate the extent of virus removal. The Takagi composition is said to satisfy this element because certain column chromatography steps are said to remove some viruses. Consequently, Takagi is said to teach each element of the claimed invention.

Applicants disagree that the specification is unclear with respect to the degree of virus removal in the presently claimed preparations. The specification makes clear that viral removal or inactivation results in preparations that are "virus safe" (4th line of text from the end of page 6). In discussing virus inactivation and virus removal, the specification also refers to several methods that can be utilized to achieve this goal and obtain virus safe compositions (see paragraph bridging pages 6 and 7). While the cited references are in German, English language equivalents of several of these references are enclosed. It is clear from these, that the methods

are useful in obtaining pharmaceutical preparations that can be safely administered for therapeutic use. This then is what is meant by virus removal or virus inactivation. The independent claims have been amended to clarify this. New claims 72 and 73 further specify that the preparations are suitable for parenteral administration. This means to those skilled in the art that the preparation is sterile and thus can safely be administered, for example, intravenously, subcutaneously, intramuscularly and by intramedullary injection (see, e.g., Stedman's Medical Dictionary (1995), 26th ed., Williams and Wilkins, Philadelphia, page 1300; copy enclosed).

There is no evidence that the Takagi preparations are sufficiently free of viruses to be safely administered for therapeutic use or that they are suitable for parenteral administration. While the Office Action suggests that the SDS-PAGE gel shown in Figure 1 of Takagi evidences a lack of virus, this is at best speculation. Those skilled in the art know that low-level amounts of protein often do not appear on SDS-PAGE gels, especially using a relatively insensitive procedure such as staining with Coomaasie Blue dye. Even though present at a relatively low level, viruses present at such levels could be sufficient to cause severe infection. Appropriate evidence concerning presence or absence of virus would be results from a viral titer, for example. Using PAGE gels is not an accepted procedure for determining whether viral concentration is sufficiently low so a preparation can safely be used in therapeutic applications. Applicants reiterate that when making an inherency argument, as here, the burden is on the Patent Office to show that any missing element is *necessarily* present in the reference. It is not enough to establish inherency by *probability or possibilities*; at best, this is all that the arguments in the Office Action provide. Accordingly, it is requested that this ground of rejection be withdrawn.

V. Claim Rejections under 35 U.S.C. 103

A. Examiner's Rationale

Claims 31, 32, 35-37, 39-40, 43-44 and 64-71 all stand rejected as obvious over Leyte and Takagi in view of Burnouf and Wise. The Examiner specifically contends that Leyte, Takagi, Burnouf and Wise all teach that vWF propeptide and pro-vWF were known, as well as

methods for making these peptides. Burnouf is said to discuss methods for achieving viral inactivation. A combination of these teachings is said to yield the currently claimed invention.

The Office Action argues that one would be motivated to combine these references in part because virus inactivation or elimination would make a safer composition for administration to a patient. Leyete is also said to discuss the importance of vWF propeptide in the expression of a functional Factor VIII binding site on vWF, which association is known to be important in maintenance of haemostasis. Further, Wise is said to discuss the importance of vWF propeptide in the process of multimer formation of vWF, a process that if disrupted is said to be associated with various blood clotting disorders. It is then concluded that one of ordinary skill would have been motivated to administer vWF propeptide to a patient to treat diseases associated with the absence of multimeric forms of vWF, or that arise due to poor interaction between factor VIII and vWF. It is further argued that one of ordinary skill would have had an expectation of success with such treatment methods because of the known biological activities of vWF propeptide just described.

B. No Motivation to Combined the Cited References

An obviousness rejection cannot stand "without also providing evidence of the motivating force that *impels* one skilled in the art to do what the patent applicant has done (Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) (emphasis added). The reasoning regarding motivation as set forth in the Office Action, however, makes several erroneous assumptions regarding the activity of vWF. As such, it fails to provide the evidence that would *impel* one to make the combination proposed in the Office Action. Rather a correct understanding negates the proposed motivation.

The first Office Action rationale assumes that injection of vWF-propeptide or pro-vWF into the plasma of a patient will increase multimerization of vWF into active high-molecular weight multimers (page 13, last 6 lines). This assumption, however, is inconsistent with the teachings of the literature. Wise, for instance, points out that assembly of vWF multimers occurs *intracellularly* in the Golgi (Wise, page 229, col. 1, lines 2-4), not in the circulation as proposed in the Office Action. Wagner supports Wise with regard to this feature

of the multimerization process (see, e.g., page 158, col. 1, third to last sentence of first paragraph under "Discussion"). This proposed motivation further assumes that vWF propeptide and vWF associate in the circulation. As already described above in addressing the Burnouf rejection, the teachings in Wise and Wagner demonstrate that this is not the case. These two peptides instead act independently of one another following secretion into the circulation. With knowledge that vWF propeptide promotes multimerization in the Golgi rather than the circulation and that pro-vWF and vWF propeptide are not even believed to interact in the circulation, one of ordinary skill would not be motivated to administer pro-vWF or vWF propeptide as a means to achieve the benefits proposed in the Office Action.

The second proposed rationale, namely that one would be motivated to administer pro-vWF or vWF propeptide to promote an interaction between vWF and vWF propeptide so a functional Factor VIII binding site could be formed, also incorrectly assumes that vWF propeptide and vWF interact in the circulation. This assumption is at odds with the antibody results of Wise discussed above with respect to the Burnouf rejection. It is also contrary to the independent role for secreted vWF which Wagner explicitly sets forth:

"In contrast to their common *intracellular* path, vWf and its propolypeptide [i.e., vWF-propeptide] separated after secretion from endothelial cells." (Wagner, at page 1958, col. 1, first sentence of second paragraph; emphasis added).

"Even in the soluble fraction the two proteins appeared to be independent of each other." (Id., at page 1958, sentence bridging col. 1 and col. 2).

For convenience, the Wagner's conclusion is reiterated here, namely that "[b]ecause of the separate fate of vWf and its propolypeptide *after secretion*, if a role in hemostasis for the propolypeptide were to be found, it is likely to be independent of vWF." (Id. at page 1958, col. 2, last sentence; emphasis added).

The collective teachings of Wise and Wagner then directly negate the assumption in the Office Action that injected vWF propeptide could be assumed to associate with vWF to facilitate an appropriate binding site for Factor VIII.

Turning to address specifically the issue of motivation with respect to the proposal for administering pro-vWF into a patient's circulation, Applicants point to the extensive evidence set forth above with respect to the Burnouf rejection demonstrating that pro-vWF is rapidly degraded so it rarely can even be detected in the circulation. Thus, one would not be motivated to administer pro-vWF because it would not be expected to last sufficiently long to have a beneficial effect.

To summarize, the combined teachings in the art suggest that administration of pro-vWF or vWF propeptide would likely have little if any utility in achieving the goals proposed in the Office Action. It thus follows that there would be no motivation to make the combination for the reasons set forth in the Office Action. Accordingly, Applicants respectfully submit that this ground of rejection should be withdrawn.

C. No Expectation of Success Even if References Combined

One of ordinary skill after reviewing the evidence of record would have concluded at the time of the invention that:

(a) administration of pro-vWF would not be expected to be of therapeutic value because of its very rapid degradation; and

(b) administration of vWF propeptide would be of limited value because: (i) it has a relatively short half-life once secreted into the circulation, and (ii) it would not be expected to interact with vWF in the circulation; so it would not be expected to play a role in vWF multimerization or in the formation of a Factor VIII binding site.

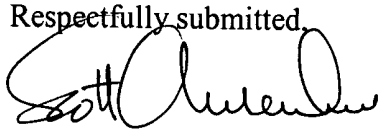
One of ordinary skill in the art after considering such evidence would thus not expect that administration of either pro-vWF or vWF propeptide would have a beneficial effect. The absence of a reasonable expectation of success means that the claims are not obvious over the combined references set forth in the Office Action.

VI. Marked Up Copy

A "Version with Markings to Show Changes Made" is provided as Appendix A. Appendix B provides a list of all the pending claims following entry of this amendment.

If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 303-571-4000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 31 has been amended as follows:

31. (Three times amended) A pharmaceutical preparation for treating blood coagulation disorders, said preparation comprising von Willebrand Factor (vWF) propeptide and having been treated for at least one of virus inactivation and virus removal so the preparation is suitable for therapeutic administration.

Claim 32 has been amended as follows:

32. (Once amended) A preparation as set forth in claim 31, said preparation ~~being essentially comprised~~ consisting essentially of vWF propeptide.

Claim 67 has been amended as follows:

67. (Once amended) A pharmaceutical preparation for treating blood coagulation disorders, said preparation comprising pro-von Willebrand Factor (pro-vWF) and having been treated for at least one of virus inactivation and virus removal so the preparation is suitable for therapeutic administration.

The following new claim 72 has been added:

72. (New) A pharmaceutical preparation as set forth in claim 31, wherein the preparation is formulated for parenteral administration.

The following new claim 73 has been added:

73. (New) A pharmaceutical preparation as set forth in claim 67, wherein the preparation is formulated for parenteral administration.--

APPENDIX B
PENDING CLAIMS

31. (Three times amended) A pharmaceutical preparation for treating blood coagulation disorders, said preparation comprising von Willebrand Factor (vWF) propeptide and having been treated for at least one of virus inactivation and virus removal so the preparation is suitable for therapeutic administration.

32. (Once amended) A preparation as set forth in claim 31, said preparation consisting essentially of vWF propeptide.

33–34. Canceled.

35. A preparation as set forth in claim 31, further comprising a hemostasis protein.

36. A preparation as set forth in claim 35, wherein said hemostasis protein is a blood factor.

37. (Once amended) A preparation as set forth in claim 36, wherein said blood factor is selected from the group consisting of mature vWF, factor VIII, activated blood coagulation factors, and blood factors with factor VIII inhibitor bypassing activity.

38. Canceled.

39. A preparation as set forth in claim 31, further comprising a platelet component.

40. A preparation as set forth in claim 39, wherein said platelet component is at least one component selected from the group consisting of collagen, a platelet glycoprotein, a platelet, fibrinogen, fibrin, heparin and a derivative thereof.

41. (Once amended) A preparation as set forth in claim 31, further comprising a phospholipid.

42. Canceled.

43. A preparation as set forth in claim 31, further comprising a pharmaceutically acceptable carrier.

44. A preparation as set forth in claim 31, wherein said vWF propeptide is a recombinant vWF propeptide.

45-63. Drawn to non-elected invention.

64. A preparation as set forth in claim 31, wherein the vWF propeptide is at least 90% pure.

65. A preparation as set forth in claim 31, wherein the vWF propeptide is at least 95% pure.

66. A preparation as set forth in claim 31, further comprising at least two components, wherein the components are selected from the group consisting of a blood factor, a platelet component and a phospholipid.

67. (Once amended) A pharmaceutical preparation for treating blood coagulation disorders, said preparation comprising pro-von Willebrand Factor (pro-vWF) and having been treated for at least one of virus inactivation and virus removal so the preparation is suitable for therapeutic administration.

68. A preparation as set forth in claim 67, wherein said pro-vWF is a recombinant pro-vWF.

69. A preparation as set forth in claim 67, further comprising factor VIII, said pro-vWF being complexed to said factor VIII.

70. A preparation as set forth in claim 67, wherein the pro-vWF is at least 90% pure.

71. A preparation as set forth in claim 67, wherein the pro-vWF is at least 95% pure.

72. (New) A pharmaceutical preparation as set forth in claim 31, wherein the preparation is formulated for parenteral administration.

73. (New) A pharmaceutical preparation as set forth in claim 67, wherein the preparation is formulated for parenteral administration.